I. REMARKS

A. Status of the Claims

Claims 1 – 16, Claims 18-30, Claims 35 -36, and Claims 49-53 are pending in the Application.

Claims 31-34 and 37-48 were previously cancelled and Claims 17, 21, and 23 are cancelled herein..

The dependent claims pending in this Application are all amended to recite a "The method" instead of "A method".

The amendment s to the claims made herein are fully supported by the specifications and claims as originally filed.

B. Petition for Extension of Time

Accompanying this Response is a Petition for Extension of Time (PTO/SB/22) for a 3-month extension as well as the required fee.

II. REJECTION UNDER 35 USC §112, 2nd PARAGRAPH REJECTION

Claims 1, 14, 16, 18, 20, 21, and 24 are rejected under Section 112, 2nd paragraph on the grounds that these claims are indefinite because it is unclear that the liquid comprising biologically compatible polymer supplied to the liquid outlet is the same liquid issuing from the outlet. The claims are amended to make it clear that the liquid that is supplied to the outlet is the same liquid that issues or exits from the outlet.

Claim 1 is rejected under Section 112, 2nd paragraph on the ground that Claim 1 is indefinite because the language "... selecting a size of the gaps... and a size of the fibre diameter..." is indefinite as it infers there are other sizes present. Claim 1 is amended herein to require a fibre diameter of μm from 0.2 μm to 100 μm and a gap size of 2.0 μm to 500 μm.

Claim 14 is rejected as being indefinite under Section 112, 2nd paragraph because Examiner believes the recitation, "...selecting a size of the gaps ..." is unclear. Claim 14 is amended to require a specific gap size.

Claim 16 is rejected because the language "selecting a fiber diameter and a gap between fiber portions" is indefinite as it infers there are other sizes present. Claims 16 is amended to require a specific fiber diameter and gap size.

Claim 18 is rejected as being indefinite because it is unclear that the fiber diameter is limited solely to the selected size given. Claim 18 is further rejected as being indefinite by the recitation of "... selecting of the fibre diameter and gaps resulting, after a period of time, in the cells having a morphology resembling nerve cells." Claim 18 is cancelled herein thus obviating this rejection.

Claims 20 and 21 and dependent Claim 15 are rejected as being indefinite on the grounds that it is unclear that the fiber diameter and gap size are limited to any particular fiber diameter or gap size. Claims 20 and 21 are amended to require a specific fiber diameter and gap size be selected to facilitate cell processes. It is believed that the amendments to Claims 20 and 21 are overcome by the amendment.

Claim 24 and dependent Claim 26 are rejected as being indefinite on the grounds that the recitation of "selecting a fibre diameter and a gap size" is unclear because it allows for the possibility that other fibre diameters and gap sixes are possible. Claim 24 is amended to require a particular fibre diameter and gap size. It is believed that the amendment to Claim 24 overcomes Examiner's rejection of Claim 24 and Claim 26.

III. Rejection Under 35 U.S.C §103(a)

A. First Section 103 Rejection

Claims 1-18, 20-28, 35-36, and 49-53 are rejected under 35 USC §103(a) as being unpatentable over Shastri *et al.* (WO/97/16545) in view of Coffee *et al.* (WO 98/03267), Sussman *et al.* (US 5,266,476), and Leong *et al* (US 5,686,091).

Examiner contends that Shastri discloses a method for altering regeneration, differentiation, or function of cells, wherein cells are attached to a surface comprising an electrically conducting polymer.

The polymers disclosed by Shastri are required to be electrically conducting polymers. This is necessary because growth and differentiation of nerve cells is achieved by electrical stimulation of the cells deposited on electrically conducting polymers. In the methods disclosed by Applicant, polymer fibers are formed using electrohydrodynamic means and thus, have an electric charge once they are formed. However, as soon as the fibers deposit on the target surface the charge is dissipated. The polymer scaffolds formed by Applicant's method are not charged nor are they electrically conductive. Surprisingly, Applicant is able to obtain cell growth and differentiation by choosing a specific fiber diameter and space between adjacent fibers (the gap size).

There is nothing in the teachings of the Shastri reference that suggests mammalian cell growth may be facilitated by use of a polymer fiber scaffold where the polymer fiber diameter and the space between adjacent polymer fibers are controlled.

None of the conductive polymers described by Shastri are used in the inventions of Applicant. Although Shastri (Col 8, lines 39-53) teaches that the electrically conducting polymers described by therein (See Col's 3-6) may be laminated onto or blended with other biocompatible, non-conductive polymers, there is nothing in the reference that teaches one skilled in this art that non-conductive polymers when used alone, may be used to grow nerve cells.

The Coffee reference describes the use of electrohydrodynamic ("EHD") means to produce fibers or fiber fragments or segments that are solid, or partially solid and which are sprayed on a wound or burn on a human or animal. The fibers may be bioresorbable or biodegradable and may have a biologically active agent e.g., pharmaceutical or DNA or growth factor applied to the surface of the fibers or the active biological agent may be encapsulated by the fibers.

Coffee teaches that biocompatible polymers such as polylactic acid, polyglycolic acid, polyvinyl alcohol, or polyhydroxybutyric acid may be used in the invention of Coffee. Additionally, Coffee teaches that fibrinogen, collagen, and New Skin™, as well as electret polymers may be used in the inventions of Coffee.

Coffee teaches that fiber diameters in the range of from about 10 nm to above 100 μm and typically from 10^2 to 10^4 nm may be produced.

There is no teaching or suggestion in the Coffee reference that any particular polymer is preferred for use in the invention of Coffee. In fact, non-polymers e.g., fibrin or collagen may be used in the methods of Coffee.

There is no disclosure in the Coffee reference that suggests that the diameter of an individual fiber as well as the size of the space between individual fibers is critical to the invention of Coffee. Examiner admits that this is true at page 6, second paragraph of the Office Action where it is stated that the Shastri and Coffee references "... do not expressly disclose selecting a fiber diameter and a size of the gaps between the fiber portions that facilitate a cell process."

Examiner reads the Sussman reference as disclosing "... a fibrous matrix for attachment of cells ... the pores have a particular diameter and are prepared by using fibers having diameters ranging from about 0.5 to 20 microns."

The Sussman reference describes non-woven sheets which are made from known techniques such as spin-bonding, thermal bonding, calendaring, needling, etc. Sussman

teaches that the Sussman invention lies in the particular configuration and confirmation of the material used and not in the material, *per se*. Thus, Sussman teaches at Col 6, lines 10-23 that polymers may be used as well as fiberglass, ceramics, collagen, wood pulp fibers and stainless steel.

The preferred non-woven fiber sheets of Sussman have an appearance like filter paper or tissue paper. The matrix when made of a polymer, is continuous and is preferred to have a thickness of 25 to 250 μm thick, preferably from 100-150 μm thick. The fiber diameter in the matrix ranges from 0.5 μm to 20 μm with 10 μm to 15 μm diameters being preferred. Cell growth takes place in the internal volume of the fiber matrix, that is, the cells do not grow on the fibers but rather between the fibers. None of the polymers described by Sussman are the same as the ones used by Applicant in her invention.

Sussman teaches that it is preferable to bond the non-woven fibrous matrix to a porous support sheet for the matrix which provides for dimensional stability and physical strength. The fiber scaffolds of Applicant's invention do not require a porous support sheet.

The Leong references discloses a biodegradable foam scaffold for cell transplantation featuring a continuous network of pores. The biodegradable foam is preferably made into an implant for placement in a human or animal. For example, the reference discloses (Col 6, lines 27-39) a foam bone scaffold with osteoinductive substances loaded into the foam scaffold which is seeded with bone cells and placed in a human being treated so as to form new bone material *in situ*.

The Leong reference teaches that the concentration of polymer in the solvent should be selected to yield pore diameters larger than 20 μm, for instance 20 to 100 μm. The preferred pore diameter is in the range from about 20 to 500 μm and preferably from 50 to 100 μm to be readily accessible for cell ingrowth.

There are several critical differences between the invention of the Leong reference and the invention claimed herein. The implantable structures described by Leong are formed from a foam. Although, the reference teaches the criticality of the pore size in the biodegradable foam scaffold, it does not teach any criticality for the polymer fiber diameter because the foam does not contain discrete fibers.

Examiner contends that at the time Applicant's invention was made it would have been obvious to use the polymer fiber scaffold of Coffee as the polymer serving for cell attachment of the Shastri invention. As discussed above, the Shastri reference requires that an electrically conductive polymer be used in the invention of Shastri. One skilled in this art would not have used the biodegradable polymers described by Coffee because such polymers are electrically non-conductive. There is no reason why one skilled in this art would use the biodegradable polymers of Coffee in the invention of Shastri because these polymers are not electrically

conductive. Shastri achieves his stated result by running an electrical current through the conductive polymer. The polymers must be electrically conductive.

Because the Shastri and Coffee references do not disclose selecting a polymer fiber diameter and a specific size of the space between polymer fibers (gap size) to facilitate cell growth and differentiation, Examiner relies on Sussman and Leong to fill this gap. Examiner contends that Sussman and Leong demonstrate that gap size affects cell entrance, entrance of nutrients, removal of waste products, vascularization, and nature of tissue ingrowth.

Sussman describes the use of a 3-dimensional non-woven fabric matrix useful in cell culture of anchorage dependent cells. The materials used to form the fibers or membranes of the Sussman invention are any material which is physiologically acceptable, i.e., does not alter the physiological characteristics of the cells, which is stable in the growth medium and to which the cells are capable of attachment, either with or without physical-chemical treatment such as acid wash, corona discharge or poly-D-lysine coating, to promote cell adhesion. The Sussman invention lies in the particular configuration and confirmation of the material used, and not in the material, per se. Any material or combination of materials having the above properties may be used. None of the polymers used in the matrix described by Sussman are biodegradable because the matrix must not dissolve in the cell culture medium.

The Sussman reference requires the matrix for growth of anchorage dependent cells to be highly porous and the reference teaches (Col 6, lines 45-50) that the matrix should have 40% - 95% porosity with a pore size between 10 μm to 100 μm. There is no teaching in Sussman regarding any criticality of the ratio of the cell diameter to the diameter of the fibers in the matrix. The Sussman reference does teach the criticality of the thickness of the fiber matrix and of the degree of porosity in the matrix.

The Leong reference describes a foam scaffold where the cells grow within the pores of the foam not on fibers. The average pore size is taught to be from 20 μm to 500 μm. In contrast to the Sussman matrix which is useful for cell culture and thus, is required to be non-biodegradable, the foam of Leong is required to be biodegradable.

One skilled in the art of scaffold implants would not look to the teachings of Sussman because the problems and issues associated with cell culture are different than the problems and issues associated with the development of and use of implantable, biodegradable cell scaffolds.

Examiner contends that it would be obvious to one skilled in this art to use the fiber diameters included in the range of Sussman which meet the fiber diameter limitation in Claim 6 of Applicant's claims because it would have resulted in fibrous matrix pore sizes suitable for cell entrance, entrance of nutrients, and removal of waste products.

Why would this be obvious? First of all the Sussman reference is concerned with growing cells in culture not with the production of implantable polymer scaffolds. The polymers used to produce the matrix described by Sussman must not be biodegradable while the polymers used by Applicant must be biodegradable. The preferred fiber diameters of Sussman are 10 μm to 15 μm, which is significantly larger than the fiber diameters claimed herein.

Examiner specifically rejects Claims 2-6, 8, and 9 contending that, "[g]iven that vascularization and the nature of tissue ingrowth is affected by the pore and fiber diameter sizes, the cell processes recited in the instant claims are facilitated ... it would have been obvious to have used cells of the sizes recited in Leong since such cells are suitable for seeding in scaffolds, resulting in vascularization and tissue ingrowth.

Applicant does not read Leong as teaching the size of any particular mammalian cell. However, even if this was taught by Leong, there is nothing in Leong that teaches the importance of the fiber diameter to the size of the cells to be grown. Leong is concerned with the production of foam scaffolds that do not have discrete fibers and thus, teaches nothing about the importance of the choice of a fiber diameter. Further, Leong teaches that the cells are grown in the pores of the foam scaffold not on the polymer foam. Surprisingly, Applicants have found that when cells are seeded on or applied to the scaffolds of Applicant's invention, the cells grow along the length of the fiber and not in the gaps (pores) between the fibers.

B. Second Section 103 Rejection

Claims 1-30, 35-36, and 49-53 are rejected over the references listed above and further in view of Smith et al (WO 01/27365) and Simpson et al. (WO 02/40242).

For the reasons discussed above, Applicant's claimed invention is not obvious in view of the Shastri, Coffee, Sussman, and Leong references. The citation of the Smith and Simpson references does nothing to aid Examiners' rejection of the claims as obvious.

The Smith reference describes the production of and use of a medical wound dressing. The reference teaches that any organic or aqueous soluble polymer which is bioabsorbable and biodegradable may be used. The wound dressing is formed by electrospinning in a process which is very similar to the process used by Coffee. Examples of such suitable polymers include, but are not limited to, linear poly(ethylenimine), cellulose acetate, and other preferably grafted cellulosics, poly(L- lactic acid), poly(caprolactone), poly (ethyleneoxide), and poly vinylpyrrolidone.

The medical wound dressing for protecting wounds comprises: a polymer that is at least weakly hydrophobic, a hydrophilic polymer, optionally, a pH adjusting component, and also optionally, at least one pharmaceutical or therapeutic agent. Electrostatically spun fibers ("nanofibers") used in the wound dressings of Smith have very small diameters, usually on the

order of about 3 nanometers to about 3000 nanometers, and most preferably, on the order of about 10 nanometers to about 100 nanometers.

The medical dressing of the Smith invention is microporous and breathable, but is resistant to high air flow. The pore sizes for the medical dressing produced using electrospinning techniques range from about 500 nanometers to about 1 micron, small enough to protect the wound from bacterial penetration via aerosol particle capture mechanisms. Pore sizes in this range may also hinder the passage of viral particles through the dressing to the wound.

It is respectfully contended that one skilled in this art is actually taught away from the production of a polymer fiber scaffold for growing mammalian cells because the fiber diameter and pore size of the nanofibers produced by Smith are so small as to prevent the growth of mammalian cells along the nanofibers and also to allow for passage of cell waste products and cell debris through the pores of the fiber matrix.

The Simpson reference describes electroprocessed collagen compositions as well as the use of electroprocessed collagen as an extracellular matrix for numerous functions. Smith states that there is a continuing need in biomedical sciences for biocompatible compositions that can be used in manufacturing devices for implantation within or upon the body of an organism.

The collagen may be processed with a variety of other materials including natural materials, synthetic materials, or combinations thereof. Examples of natural materials include, amino acids, peptides, denatured peptides such as gelatin from denatured collagen, polypeptides, proteins, carbohydrates, lipids, nucleic acids, glycoproteins, lipoproteins, glycolipids, glycosaminoglycans, and proteoglycans. Examples of synthetic matrix materials for electroprocessing with collagen include, but are not limited to, polymers such as poly(lactic acid) (PLA), polyglycolic acid (PGA), copolymers of PLA and PGA, polycaprolactone, poly(ethylene-co-vinyl acetate), (EVOH), poly(vinyl acetate) (PVA), polyethylene glycol (PEG) and poly(ethylene oxide) (PEO) and drugs,

The reference acknowledges that polymer matrices are known in the art but suffer the drawbacks associated with their chemical and structural dissimilarities with natural materials. Fibrotic encapsulation, lack of cellular infiltration, and rejection are problems experienced by such implants. Efforts to overcome these issues have focused in part on use of biodegradable synthetic polymers as scaffolding to engineer prosthetic constructs to improve biocompatibility.

Biodegradable polymers suffer the drawback of producing major degradation by-products that, in intimate contact with to individual cells, can produce an inflammatory response and decrease the pH in the cellular microenvironment. Thus, steps must be taken to ensure proper by- product removal from the tissue-engineered construct when using biodegradable materials. Another complication is that bioabsorbable structural materials are

degraded over time, resulting in structural failure of the implant. Fibrotic encapsulation and lack of cellular infiltration also remain problems.

Simpson overcomes these drawbacks associated with synthetic implants by the use of collagen implants. Collagens are a family of proteins that are widely distributed throughout the body. This scaffolding material is one of the most prominent proteins present in animal tissue. Collagen is the principle structural element of most extracellular matrices and, as such, is a critical structural element of most tissues.

The entire emphasis in the Simpson reference is on the use of electroprocessed collagen. There is no direction to the skilled artisan about the use of electroprocessed biodegradable polymers to produce polymer scaffolds much less scaffolds having a required fiber diameter and gap size between fibers. Further, the Simpson reference expressly teaches one skilled in the art that the use of biodegradable polymer scaffolds is undesirable and thus, leads one away from such use.

The following Table summarizes the essential features of the prior art inventions in contrast to Applicant's invention.

Reference	Essential Feature of Invention	Applicant's Invention
Shastri	Describes a type of cell culture on polymers which must be electrically conductive because nerve cells growing on polymer are stimulated with an electrical current.	Polymers used in the implantable scaffold must be biodegradable and bioresorbable and are not electrically conductive.
Coffee	Describes the production of wound/burn dressings using an electrohydrodynamic means and method. Various polymers and non-polymers may be used to produce the wound dressing. Does not teach growth of any cells.	The polymer fiber scaffold claimed by Applicant is used for the growth of mammalian cells in situ when implanted in a human.
Sussman	Describes a method of cell culture for anchorage dependent cells *in vitro* using various fiber matrices. Various materials are described which may be useful to prepare the fiber matrix including polymers. No biodegradable polymers are taught because the fiber matrix formed from such polymers would dissolve or degrade in the cell culture media. ,	Applicant's invention is not directed to a cell culture and the polymer fiber scaffolds of Applicant are expressly made to biodegrade *in situ*.
Leong	Describes a rigid, biodegradable, highly porous, polymer foam scaffold for growth of cells. The cells grow in the pores of the foam and not on the fibers probably because there are not discrete fibers in a foam.	Polymer fiber scaffold used for the growth of mammalian cells in situ where the cells grow on the fibers and not in the gap space (pores) between fibers.
Smith	Describes the production of a "spray-on" wound dressing formed by electro-processing various polymer solutions including some biodegradable polymers to produce films composed of nanofibers having diameters in the 10 – 500 nm range. The wound dressing is designed to prevent the entrance of bacterial into the wound and is not suitable for supporting the growth of mammalian cells.	Applicant's invention is to a biodegradable polymer fiber scaffold used for the growth of mammalian cells in situ where the cells grow on the fibers.
Simpson	Describes the preparation of electroprocessed collagen which may be optionally processed with a variety of other materials including polymers among which are some biodegradable polymers. The electroprocessed collagen may be used for many purposes among which are support the growth of mammalian cells.	

The Shastri, Sussman, and Simpson references are concerned with various ways to grow cells in cell culture. None of these references teaches one skilled in the art to use biodegradable polymer fiber matrices in cell culture much less to prepare the implantable,

biodegradable polymer fiber scaffolds of Applicant's invention. Coffee and Smith describe the production and use of wound dressings. One skilled in this art would not be led by the disclosures of either of these references that one could use the wound dressings described therein for mammalian cell growth. Only Leong describes a porous, foam polymer scaffold suitable for growing cells in situ when implanted into a human. Foam structures are very different from fiber mats or webs. The cells seeded onto the foams of Leong grow in the pores. In contrast, mammalian cells seeded onto Applicants polymer scaffolds grow on the fibers.

It is respectfully asserted that none of the references taken individually or collectively render Applicant's claimed invention obvious within the meaning of Section 103(a).

IV. Conclusion

Based on the amendments and arguments made herein, it is respectfully asserted that Examiner's rejections have been overcome and that this application is in condition for allowance. Examiner is respectfully requested to withdraw all rejections and to issue a Notice of Allowance. If there are any questions regarding these amendments and remarks, Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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